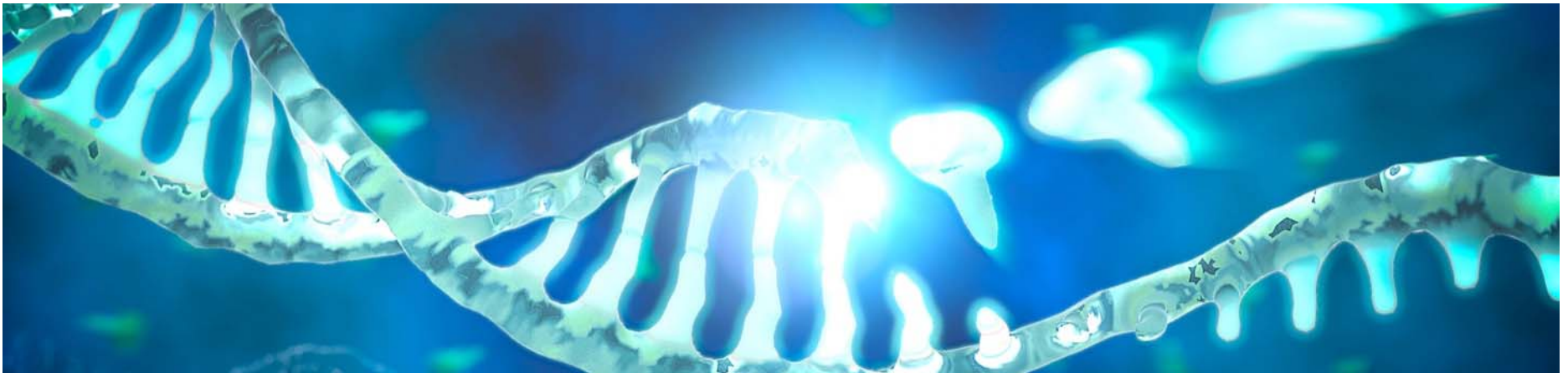


# Using AI to Improve the Safety of New Drug Candidates

**Nigel Greene**  
Streamlining Drug Discovery

18 October 2018



# Outline

- Why safety?
- What are key causes of safety failures?
- How will artificial intelligence help?
- Where are the key gaps?



# Safety Failures in the Clinic

2006

The New York Times

April 8, 2009

## British Rethinking Rules After Ill-Fated Drug Trial

By ELISABETH ROSENTHAL

In February, when Rob O. saw the text message from Parexel International pop up on his cellphone in London — “healthy males needed for a drug trial” for £2,000, about \$3,500 — it seemed like a harmless opportunity to make some much-needed cash. Parexel, based in Waltham, Mass., contracts with drug makers to test new medicines.

Just weeks later, the previously healthy 31-year-old was in intensive care at London’s Northwick Park Hospital — wires running directly into his heart and arteries, on dialysis, his immune system, liver, kidneys and lungs all failing — the victim of a drug trial gone disastrously bad.

One of six healthy young men to receive TGN1412, a novel type of immune stimulant that had never before been tried in humans, Rob O. took part in a study that is sending shock waves through the research world and causing regulators to rethink procedures for testing certain powerful new drugs.

CD28 Agonist

Preclinical

2016

BBC NEWS

Home UK World Business Politics Tech Science Health Education Entertainment

World Africa Asia Australia Europe Latin America Middle East US & Canada

## France clinical trial: 90 given drug, one man brain-dead

© 15 January 2016 - Europe



FAAH Inhibitor

Phase I

2006

The New York Times

World U.S. NY REGION BUSINESS TECHNOLOGY SCIENCE HEALTH SPORTS OPINION

FITNESS & NUTRITION HEALTH CARE POLICY MENTAL HEALTH

## End of Drug Trial Is a Big Loss for Pfizer



PHILIP HODGSON FOR THE NEW YORK TIMES

The same cause to Pfizer's chief scientist, Dr. John I. LaManna, as he was speaking at 7 a.m. Saturday: the company's most promising experimental drug, intended to treat heart disease, actually caused

CETP Inhibitor

Phase II

2004

BBC NEWS

LIVE - BBC NEWS CHANNEL

Last updated: Thursday, 30 September, 2004, 15:42 GMT 16:42 UK

E-mail this to a friend

Printable version

## Arthritis drug removed for safety

Drug company Merck has removed its arthritis painkiller Vioxx because of data showing an increased risk of heart attack and stroke.



Patients currently taking the drug should contact their doctor to discuss stopping and switching to alternative treatments, experts said.

Around 9 million people in the UK have arthritis

A three-year trial showed an increased risk of cardiovascular events began after 18 months of Vioxx treatment.

COX2 Inhibitor

Post-Approval



# 5R framework increased the R&D productivity

## Right target

- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

## Right tissue

- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

## Right safety

- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity and drug–drug interactions
- Understanding of target liability

## Right patient

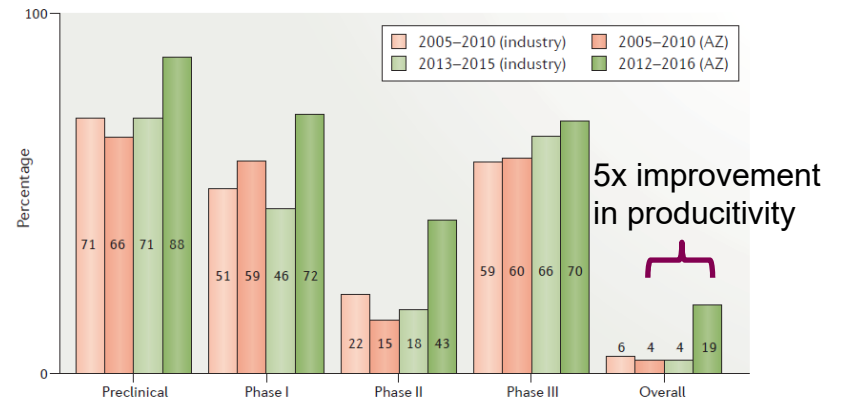
- Identification of the most responsive patient population
- Definition of risk–benefit for a given population

## Right commercial potential

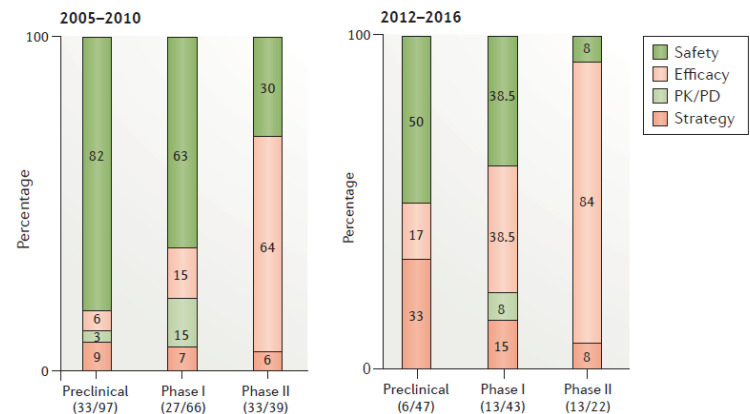
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostics and biomarkers

*Impact of a five-dimensional framework on R&D productivity at AstraZeneca*  
 P. Morgan, et al; Nature Reviews Drug Discovery 17, 167–181 (2018)

a Project success rates



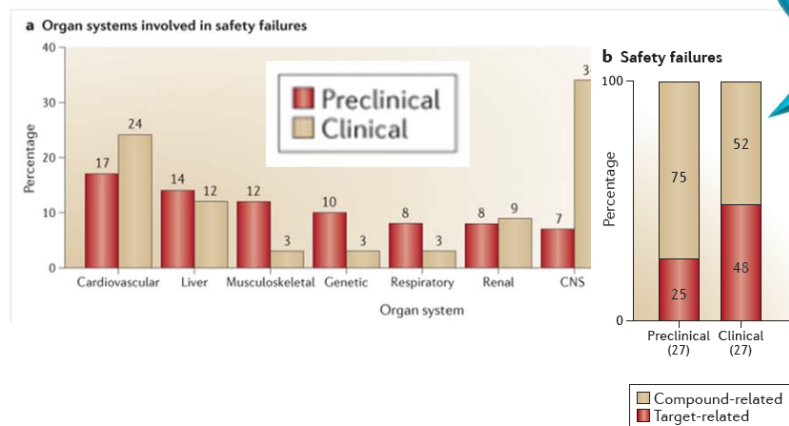
b Reasons for failure



# What is Causing Safety Failures

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework.  
D. Cook, et al; Nature Reviews Drug Discovery **13**, 419–431 (2014)

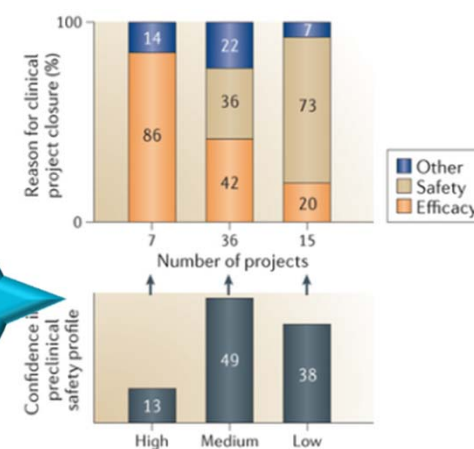
## Safety causes for candidate drug terminations



Numerous causes of safety attrition, predominantly compound related

More likely to succeed when high confidence in preclinical safety

## Confidence in safety

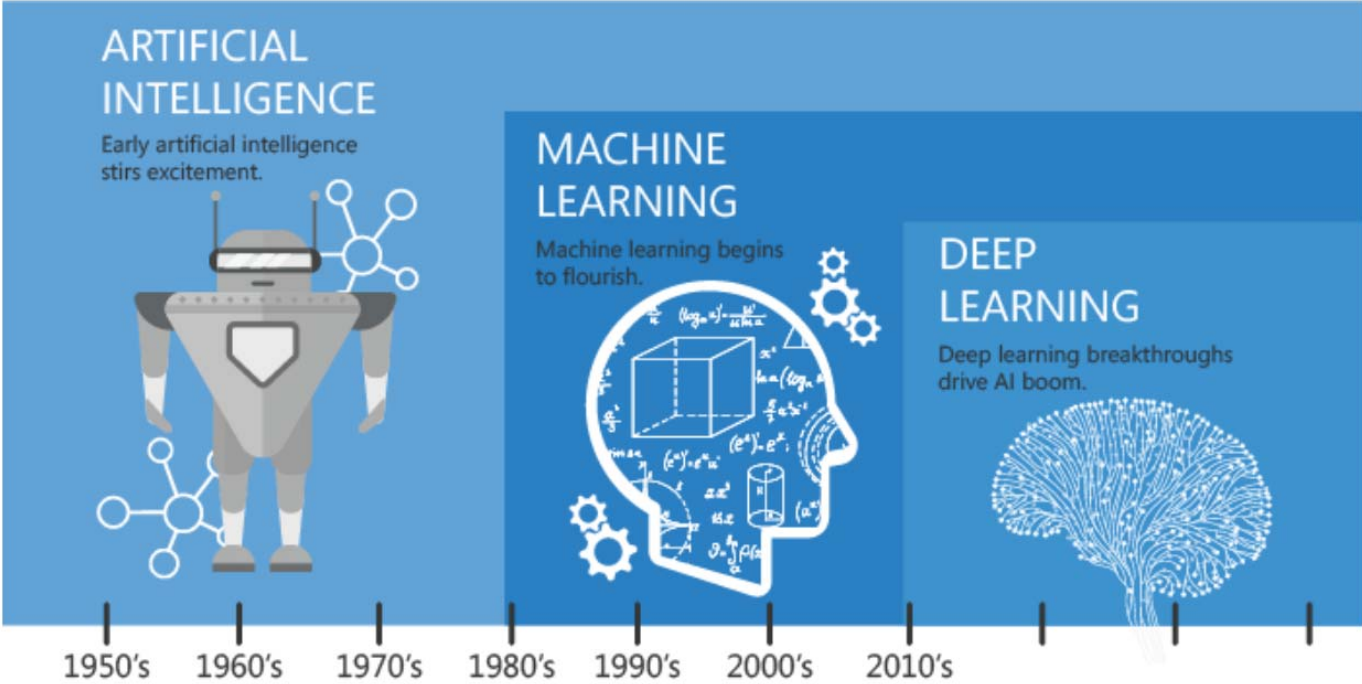


**Build confidence in safety at the point of design**

Once a chemical is synthesized, its properties are, for the most part, fixed. All that remains is to discover what they are.



# Machine Learning and AI



Since an early flush of optimism in the 1950's, smaller subsets of artificial intelligence - first machine learning, then deep learning, a subset of machine learning - have created ever larger disruptions.



# So what's the big deal about AI?

The screenshot shows the top of a Nature news article. The header includes the Nature logo and navigation links like 'MENU', 'Search', 'E-alert', 'Submit', and 'Login'. Below the header, there are navigation tabs for 'News & Comment' and 'Research'. The article title is 'Software beats animal tests at predicting toxicity of chemicals', dated 11 July 2018. The sub-headline reads 'Machine learning on mountain of safety data improves automated assessments.' The author is Richard Van Noorden. There are social media icons for Twitter, Facebook, and Email. A 'PDF version' link is visible. Below the main image, there are 'RELATED ARTICLES' including 'Legal tussle delays launch of huge toxicity database', 'How to design a safer chemical', and 'Why the historic deal to expand US chemical regulation matters'. The main image shows a white rat in profile against a dark background.

**NEWS** · 11 JULY 2018

## Software beats animal tests at predicting toxicity of chemicals

*Machine learning on mountain of safety data improves automated assessments.*

[Richard Van Noorden](#)

[Twitter](#) [Facebook](#) [Email](#)

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**RELATED ARTICLES**

- [Legal tussle delays launch of huge toxicity database](#)
- [How to design a safer chemical](#)
- [Why the historic deal to expand US chemical regulation matters](#)

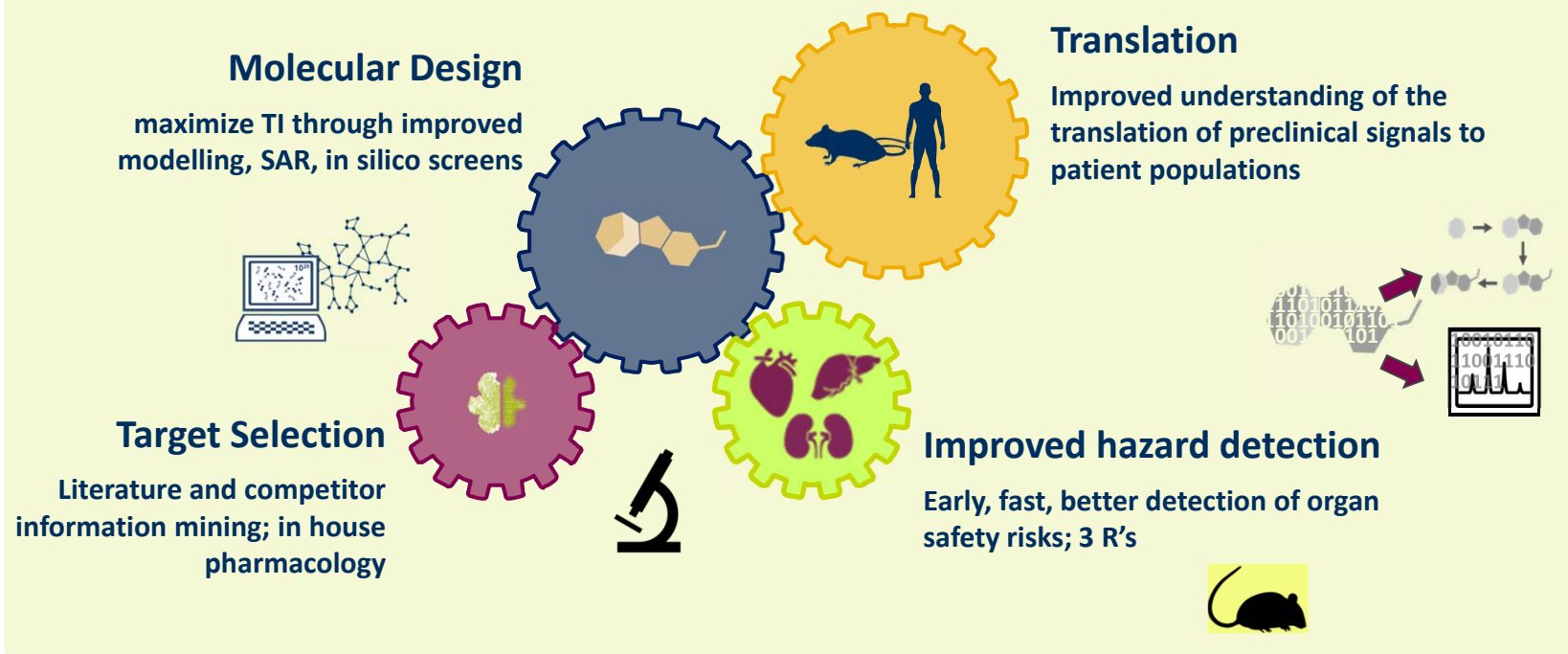
Computer programs can, in some cases, predict chemical toxicity as well as tests done on rats and other animals. Credit: Coneyl Jay/SPL

- Artificial Intelligence has the capability to transform drug safety
- Need to separate the reality from the hype



# Areas for investment in Artificial Intelligence

AI IS BECOMING THE FOUNDATION OF ACCELERATED, LARGE SCALE COMPUTATIONAL ANALYSIS AND INTEGRATION



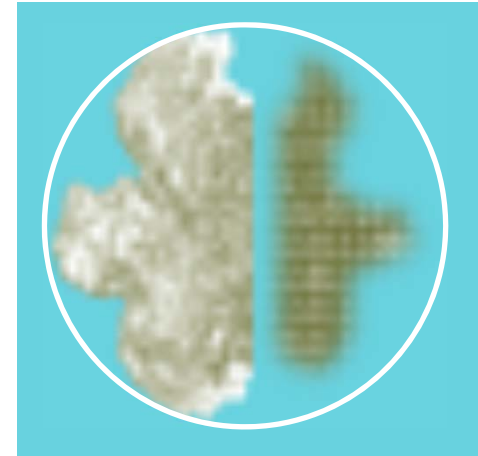
The impact of AI will come from big data analysis, modeling and image analysis



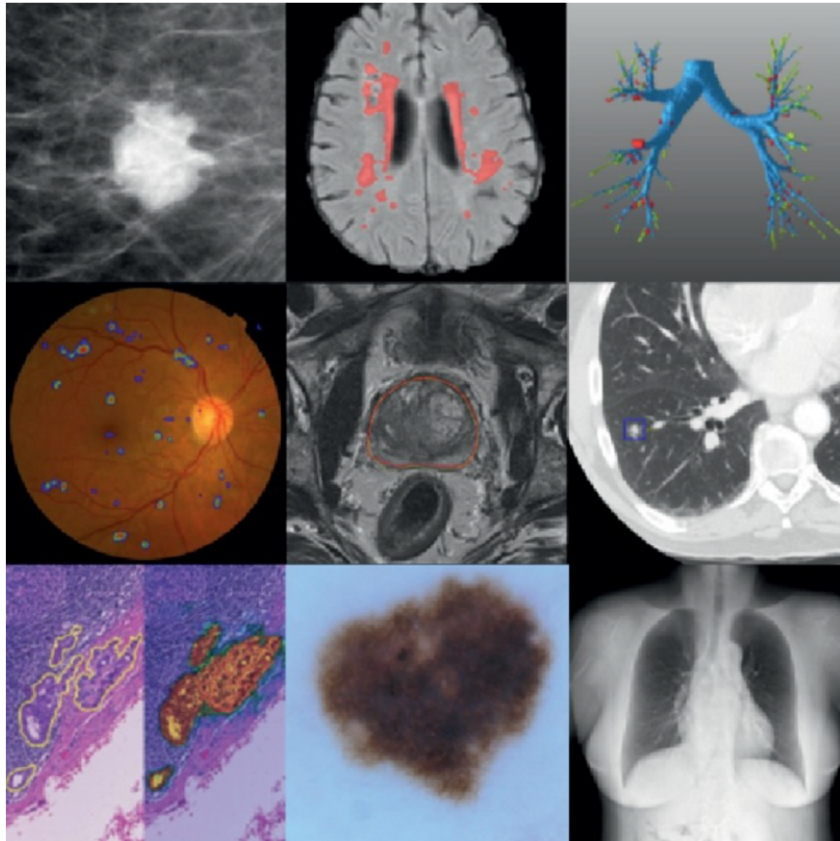


# Target Identification & Selection

- Choose the right target
- Understand the broader risks of modulating a target
- Using AI for literature and competitive intelligence mining by NLP
- Drug target liability scoring from knowledge graphs vs major organs according to patient context



# Hazard Detection



Collage of some medical imaging applications in which deep learning has achieved state-of-the-art results.

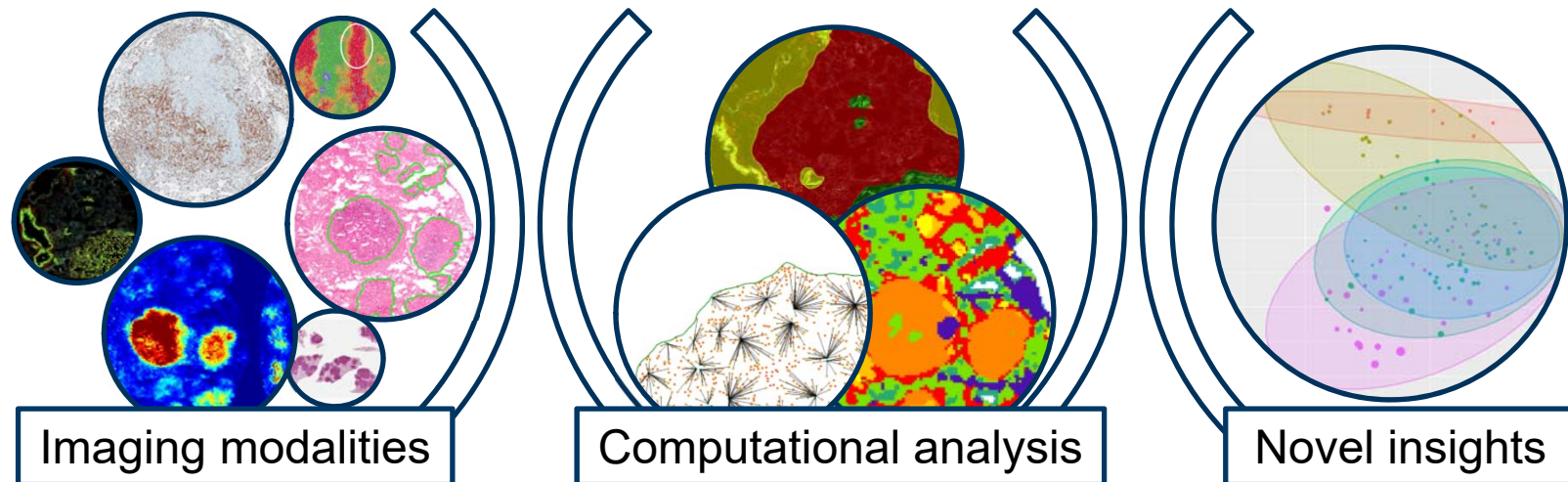
From top-left to bottom-right:

1. mammographic mass classification
2. segmentation of lesions in the brain,
3. leak detection in airway tree segmentation,
4. diabetic retinopathy classification
5. prostate segmentation,
6. nodule classification,
7. breast cancer metastases detection,
8. skin lesion classification
9. bone suppression



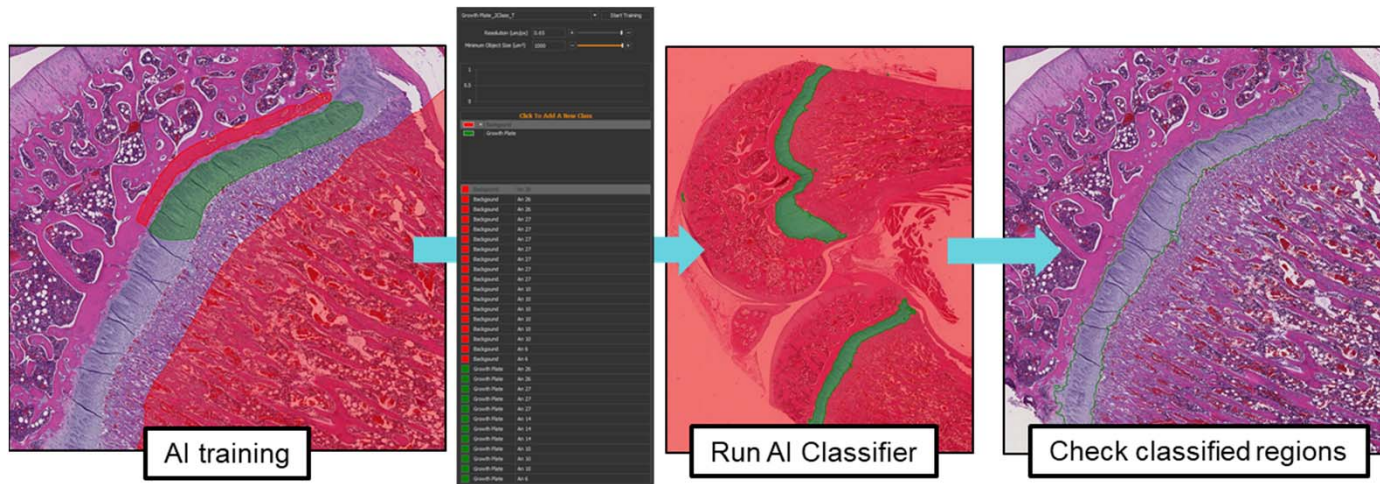
# AI in Pathology Studies

- Different approaches for different problems
- Consistency over large data sets and studies
- Big data generation will enable insights that are greater than the sum of the parts



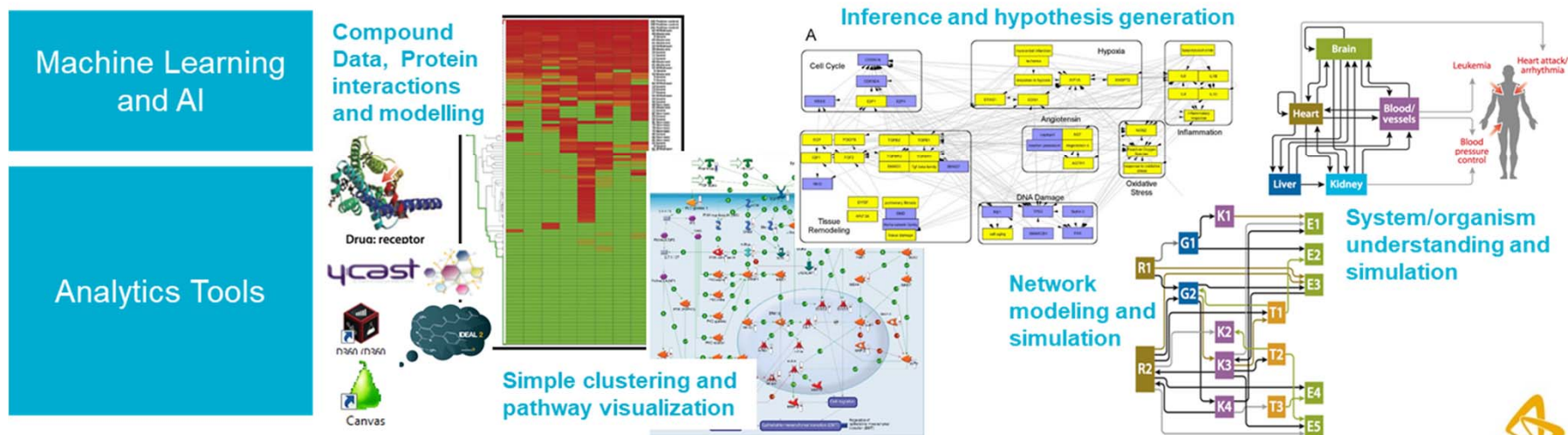
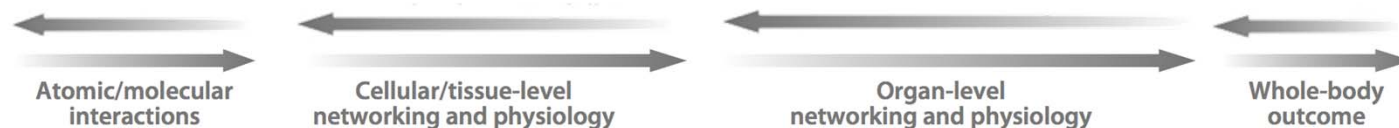
# Using AI in Pathology

- ~80% of tissue slices read from a study are “normal”
- Using image analysis and Deep Learning it will be possible to reduce the time taken to read a study
- Data storage, however, will be non-trivial. Estimate 1.5TB of images per year.



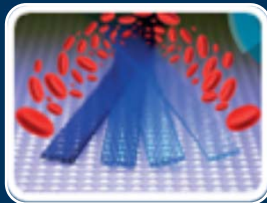
# Translation

- The ability to put the safety signals we see preclinically into context with knowledge of the patient



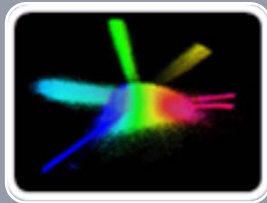


# Artificial Intelligence in Drug Discovery



## Productivity

- Prosecuting more projects without a linear increase in cost



## Exploring more chemical space in the hunt for the **best** leads

- Greater opportunity for exploration over exploitation



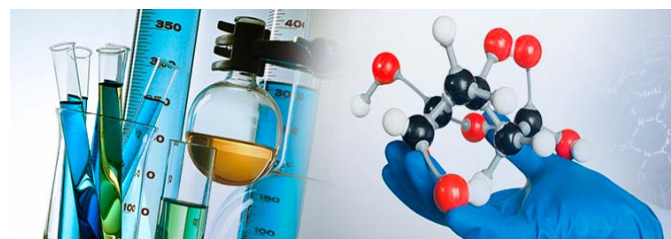
# Applications of AI in Molecular Design

**What to make next?**



**De novo design**

**How to make it?**

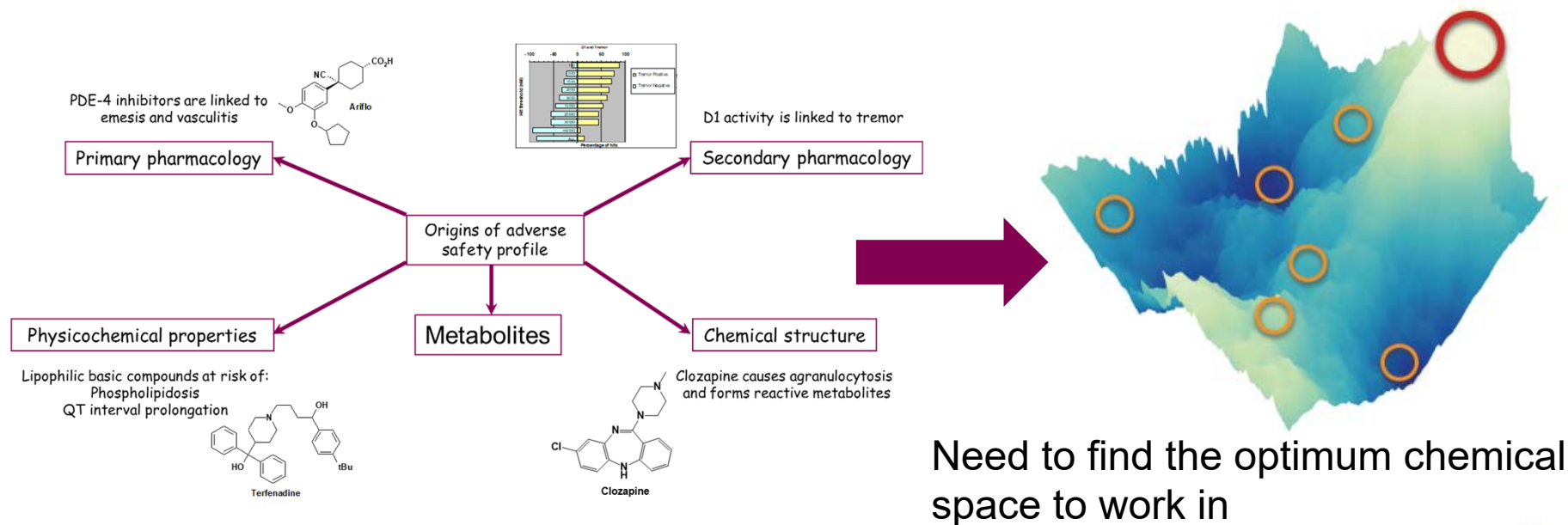


**Synthesis planning**



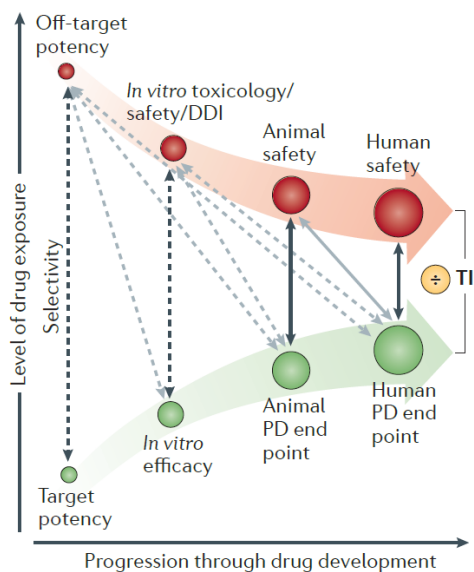
# Molecular Design

- Drug discovery is a multi-parameter optimization problem
- Balance of efficacy/potency, ADME and safety





# Therapeutic index is often uncertain



Muller & Milton (2012). Nat Rev Drug Discovery



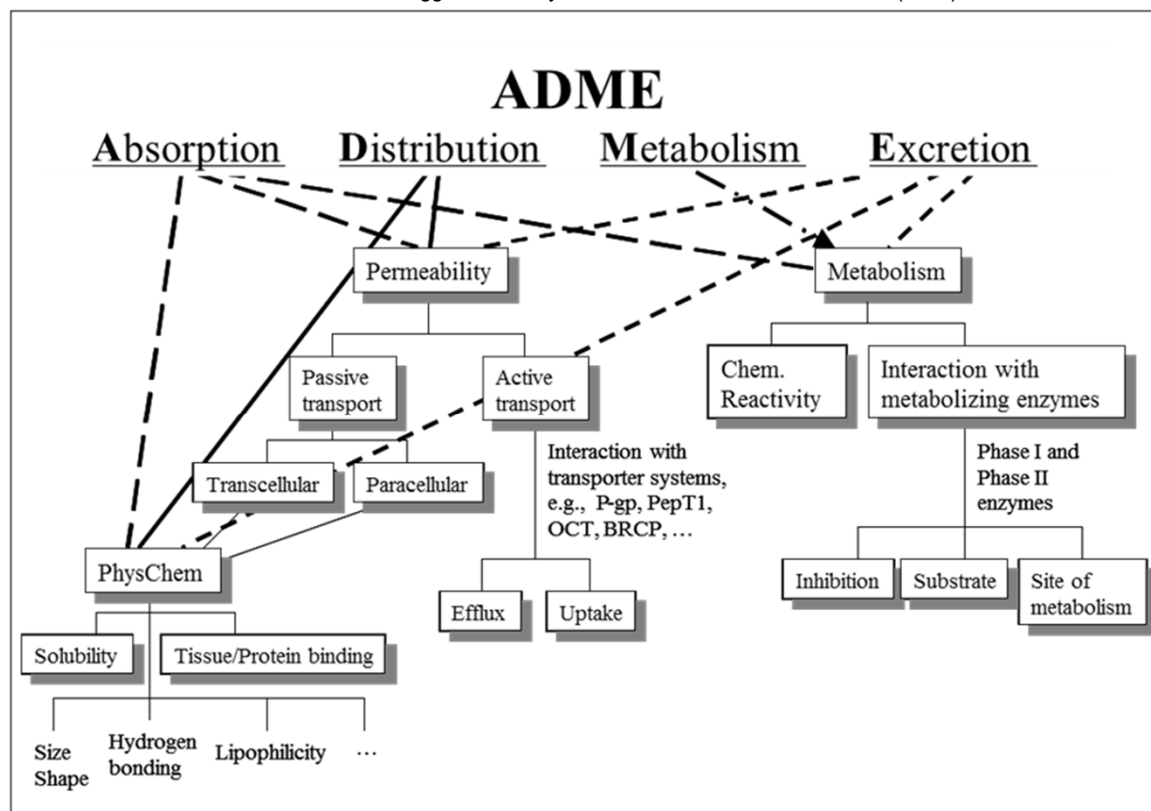
Find *productive* chemistry space early

**The safety and efficacy of a drug candidate needs to be well balanced**



# Absorption-Distribution-Metabolism-Excretion (ADME)

adapted from S.Winiwarter et al. *Use of Molecular Descriptors for ADME Predictions*. Compr. Med. Chem. II, D.J.Triggle & J.B.Taylor, Eds., Vol. 5, Elsevier, 531-554 (2007)



# Key Gaps

Accurate prediction of human PK will lead to:

- Better understanding of clinical feasibility
- Better estimates of therapeutic index
- Better use of resources in producing clinic-ready material

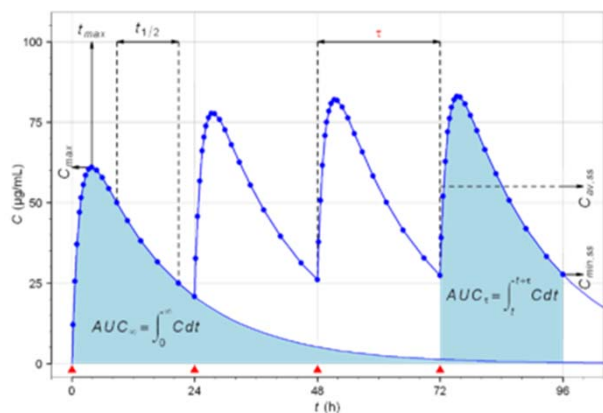
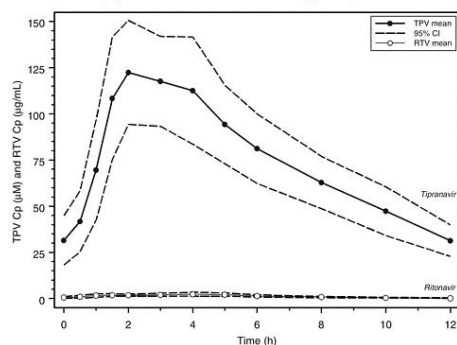


Figure 1 Mean Steady State Tipranavir Plasma Concentrations (95% CI) with Ritonavir Co-administration (tipranavir/ritonavir 500/200 mg BID)



## Summary

- Data, and the knowledge gained from it, are one of a company's most valuable asset
- The volume of data generation is growing almost exponentially and is rapidly outstripping our capacity to digest all the information
- Artificial intelligence will enable us to exploit and maximize the value we get from our data
- Drug discovery is a multi-parameter problem that requires the ability to think in multiple dimensions
- Safety, ADME are as (more) important as efficacy/potency



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David Price

Russ Naven

Bill Pennie

Kevin Dack

Julian Blagg

Chris Bouton

... and many, many more



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